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14. ABSTRACT

The research program commenced 1 November 2000 and terminated 14 January 2004. Progress was achieved in a broad range of areas, including (1) radiosurgery treatment planning; (2) stochastic network approximations for improving air operations planning; (3) basis pursuit; limited-memory solution of complementarity problems; (4) solution of MPECs via nonlinear programming; (5) supporting research in optimization methods. This progress is described in more detail in Section 3. This work was described and documented in a total of 46 research papers and 2 doctoral theses. These papers, with their status as of the end of the reporting period, are listed in Section 5.

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This is the final progress report on AFOSR Grant F49620-01-1-0040 to the University of Wisconsin-Madison. The principal investigators (PI) were Michael C. Ferris and Stephen M. Robinson, and the period of performance was 1 November 2000 – 14 January 2004.

1. Objectives

The objectives of the research effort have not changed from those stated in the proposal. The principal research tasks are summarized here for later reference:

1. Improvement and extension of the capabilities of a prototype optimization-simulation linking system developed under a predecessor AFOSR award
2. Applying optimization techniques for inverse treatment planning in radiosurgery applications, particularly for treatment of tumors, vascular malformations, and pain disorders within the head
3. Development and application of stochastic optimization methods for various facets of the air mobility optimization problem

2. Status of Effort

The research program commenced 1 November 2000 and terminated 14 January 2004. Progress was made in several areas, described in more detail in Section 3. This work was described and documented in a total of 46 research papers and 2 doctoral theses. These papers, with their status as of the end of the reporting period, are listed in Section 5.

3. Accomplishments/New Findings

As is detailed in Section 5, work under this grant resulted in the production of 46 papers. In this section we describe several of the most important areas of work that produced those papers, indicating the progress achieved and the papers resulting from that progress.

3.1. Radiosurgery treatment planning

An area of continued emphasis throughout the period of this grant was the efficient and effective planning of radiosurgery treatments, in which the delivery of focused doses of radiation replaces or supplements traditional surgical methods. We will describe this work in three subsections below, according to differing treatment methods and contexts to which the work applied.

3.1.1 Gamma Knife Radiosurgery

The Gamma Knife is a highly specialized treatment unit that provides an advanced stereotactic approach to the treatment of tumors, vascular malformations, and pain disorders within the head. Inside a shielded treatment unit, beams from 201 radioactive sources are focused so that they intersect at the same location in space, resulting in a spherical region of high dose referred to as a shot of radiation. The location and width of the shots can be adjusted using focusing helmets. By properly combining a set of shots, larger treatment volumes can be successfully treated with the Gamma Knife.

An important goal of our project was to automate the treatment planning process by solving, for each patient, an optimization problem that generates a dose distribution conforming closely to the treatment volume. The variables in the optimization include the number of shots of radiation along with the size, the location, and the weight assigned to each. We formulated such problems

using a variety of mathematical programming models, including nonlinear programming. Our treatment planning methods are in use on patients at the University of Maryland Medical School. As described in Section 8, in November 2002 this work won the William Pierskalla Best Paper Award for research excellence in the field of health care management science.

3.1.2 Radiosurgery planning via neuro-dynamic programming

As part of the work of this grant we developed a new method for planning radiotherapy treatments, which we describe briefly here.

In radiation therapy ionizing radiation is applied to cancerous tissue, damaging the DNA and interfering with the ability of the cancerous cells to grow and divide. This radiation also damages healthy cells, but they are better able to repair the damage and to return to normal function. Since both cancerous and healthy cells are affected by radiation, dose distributions need to be designed that expose the tumor to enough radiation for treatment while at the same time avoiding excessive radiation to surrounding healthy tissue and, in particular, nearby organs.

Given a particular delivery mechanism, a treatment plan corresponds to settings of the machine that facilitate the delivery of the target dose distribution. Optimization techniques can be used to design such plans. Typically these problems are complicated due to the ever increasing complexities of the delivery mechanisms and the large amount of data that needs to be manipulated to get sufficient detail of the dose on the target area. We have designed such treatment plans in AFOSR-supported work.

While these problems remain at the forefront of cancer treatment planning and many techniques have been proposed for the large varieties of machines, many of which take from minutes to hours to solve, we will not focus in this section on this aspect of the problem. Instead, as we now describe, we will look at the day-to-day planning problem and derive target distributions that hedge against errors in the delivery process and assume the aforementioned planning tools will be used on specific machines to approximate these target distributions.

The day-to-day planning problem arises since many cancer patients are treated by a course of radiation over a period of days or weeks. For example, the full dose may be delivered in 20 or so treatments, with 1/20-th of the total dose delivered at each stage. This limits burning and gives the healthy tissue time to recover. As mentioned above, particular planning tools approximate the idealized dose, leading to errors between the planned and delivered dosage. Furthermore, in dividing the radiation dose over a series of treatments, additional errors can be introduced. Many sources can contribute errors to individual treatments, including the re-registration of the patient on the machine, the movement of the patient during treatment, and machine error. Imaging devices are currently being developed and prototyped on particular treatment devices that can measure the dose as it is being delivered, highlighting where the delivered treatment may be inaccurate. We have devised ways of exploiting this knowledge to improve the overall treatment. Our method aims to generate a deliverable plan for each treatment in the course that compensates over time for movement of the patient and error in the delivery process. To this end, we develop a control mechanism for the treatment course, leaving the implementation of the daily dosage to a specialized planning tool. To find the control, we use neuro-dynamic programming, particularly a rollout policy, to improve upon simple heuristic policies. These

techniques include neuro-dynamic programming (NDP) ideas and heuristic policies, one of which is currently in use. We also presented specific patient examples and discussed their results, showing how the NDP ideas can improve upon the heuristic policies. Finally, we showed how to define rules of thumb, which allow for immediate practical implementations of solutions suggested by NDP while still maintaining most of the improvements.

3.1.3 Conformal radiation therapy

Conformal radiation therapy (CRT) is the traditional method for delivery of radiation therapy. It is available in nearly all treatment centers (as compared to newer techniques such as IMRT, IMAT or Tomotherapy). The research issue here is whether we can deliver comparable plans to the new techniques using standard three-dimensional (3D) CRT combined with advanced optimization techniques.

We have developed an optimization framework for three-dimensional conformal radiation therapy. In this type of therapy, beams of radiation are applied to a patient from different directions, where the aperture through which the beam is delivered from each direction is chosen to match the shape of the tumor as viewed from that direction. Given a set of equi-spaced beam angles, one can formulate and solve a mixed-integer linear program to determine the most effective angles to be used in a treatment plan and the weight (exposure time) to be used for each beam. The model can be enhanced to account for the use of wedge filters, which may be placed in front of a beam to produce a gradient in beam intensity across the aperture. As far as we know, this is only technique that considers all these together.

We have developed several techniques for strengthening the formulation (and therefore reducing the solution time), as well as methods to control the dose-volume histogram implicitly for various parts of the treatment region using hot- and cold-spot control parameters. In conjunction with colleagues at Maryland we developed a testbed for generating realistic dose distributions (including consideration of inhomogeneities in material) delivered from linear accelerators. We showed the effectiveness of the proposed approach on two practical data sets. We have investigated techniques for sampling, iterative refinement and adaptation of plans.

In addition, we have developed a suite of optimization tools to facilitate radiation treatment planning within the Matlab programming environment. The data included with these tools were computed for real patient cases using a Monte Carlo dose engine. We showed how to formulate a series of optimization models using these data within a modeling system. Furthermore, we provided visualization techniques that assist in validating the quality of each solution. The versatility and utility of the tools are demonstrated using a sequence of optimization techniques designed to generate a practical solution. These tools and the associated data are available to anyone for download from http://www.cs.wisc.edu/~ferris/3dcrt.

3.2. Stochastic network approximations for improving air operations planning

Strategic airlift operations are a very important component of effective military capability for the United States. Such operations are complex, and require comprehensive planning methods to make the best use of resources. To the extent that these planning methods can be improved, the airlift operations themselves will be more effective.

One prominent current planning method is the NRMO model, developed at the Naval Postgraduate School and the RAND Corporation by Rosenthal, Williams and several co-workers. It uses deterministic linear programming to allocate airlift resources for maximum performance against specified requirements. However, the degree to which the NRMO solution gives optimal guidance for real decisions depends on how well the optimization model represents the real system.

A limitation of the original NRMO model is the assumption that no random factors exist in the system. For example, the deterministic nature of this model results in its fully utilizing the capacity of some airfields, and a requirement for repair resources to deal with maintenance problems of transiting aircraft can extend their ground times, thereby starting a cumulative blockage in the system. Such a blockage can severely degrade the system throughput. The effect of uncertainty can be studied by applying simulation to a deterministic allocation found by NRMO. However, even if the simulation suggests possible severe problems, it does not show how to adjust the deterministic allocation to overcome those problems with the least cost in resources. For that, a revision of the optimization model is needed.

Recent work of Niemi, sponsored by a predecessor AFOSR grant, showed how to incorporate stochastic elements into NRMO. The resulting stochastic version should provide increased realism in planning, because it accounts for randomness that is present in the actual system. However, even the deterministic version of NRMO is a large model, and when stochastic features are added the solution time is considerably extended. It would be helpful to have a modeling tool that could provide quick, though perhaps rough, estimates of the effect of different stochastic factors on throughput in an airlift system.

Work under this grant addressed this question by applying methods recently brought into use in manufacturing. These techniques first model the system under consideration as a network of queues, then use recently developed approximation methods to find estimates of lead time and throughput. Such estimates, though not exact, can pinpoint the location of bottlenecks and can indicate how and where additional resources could improve system performance. These methods have already had substantial success in improving the productivity of complex manufacturing operations.

In work under this grant we began with modeling experiments aimed at adapting the manufacturing approach to deal with logistical models such as airlift. One of these was presented in an invited paper for the 2001 Winter Simulation Conference, and we described another in a similar invited paper for a workshop on dynamic stochastic optimization, held in March 2002 at the International Institute for Applied Systems Analysis in Laxenburg, Austria. This paper was published in the proceedings of that workshop.

Valuable comments and guidance from personnel of AFOSR and the Air Mobility Command indicated that a focus on improvement of airfield operations could be an effective application of this technology. During the last part of the grant period computational development and theoretical progress were made on a long paper on stochastic modeling of airfield operations, for submission to the journal *Mathematical and Computer Modelling.* Actual submission was made

in March 2004, after the closing date of the grant, and it will be reported in connection with the follow-on grant.

3.3. Basis pursuit

A large body of research focuses on medical applications involving large databases of raw data. A common goal in such applications is to use the raw data for classification purposes in order to predict outcomes; another goal is selection of important variables related to the outcome (feature selection in machine language terminology). In classification, we use observations (such as blood pressure, height, weight, age, etc.) to classify patients into classes related to the outcomes (such as recurrent cancer or not, disease susceptible or not, death likely or not, etc.). In variable selection, we look for those observations that influence the outcome the most. Investigators have developed a variety of models to achieve these goals. Such models commonly involve the solution of large scale linear programs, large scale quadratic programs, and general nonlinear programs.

Our contribution to this work during this grant period was twofold:

- We showed how to process the existing models much more effectively using existing numerical optimization software.
- While traditionally the tuning of parameters in these models is carried out by trial and error, we showed how to use sampling and derivative-free optimization techniques to carry out this process.

These techniques have been applied in conjunction with the University of Wisconsin-Madison School of Nursing (Professor P. F. Brennan and Research Assistant K. Volrathongchai) to investigate their applicability to predicting falls of patients in nursing homes. We have also investigated their use for predicting whether chemotherapy is useful in classes of cancer patients (with Professor Kerr, Oxford University and Dr. Grommet, University of Birmingham). The key issue here is that some patients do not benefit from chemotherapy, so we can spare them the trauma of the treatment. This work comprises Chapter 3 of the doctoral dissertation of Meta M. Voelker.

3.4. Limited memory solution of complementarity problems

Physical simulations occurring within video games, in particular the treatment of friction, require solutions of complementarity problems. While these problems are typically small convex quadratic programs (less than 300 variables) the principal issue is how to solve them quickly (governed by frame rate) and without using much memory (governed by memory on a playstation console, for example). We have investigated the motivating problem, along with a simple interior point approach for its solution, and have explored various linear algebra issues arising in the implementation. These issues include preconditioning, ordering, and various ways of solving an equivalent augmented system.

3.5. Solution of MPECs via nonlinear programming

Constrained optimization models serve to formulate and solve many large-scale deterministic problems arising in economics. Such models include, for example, square systems of equations and nonlinear programs. More recently, researchers have considered models with constraints including complementarity requirements to model various phenomena, particularly in general

equilibria. These models have been unified in the framework of mathematical programs with equilibrium constraints (MPEC). We developed a new suite of tools for working with MPEC models. In particular, we showed how to construct and solve automatically a variety of different nonlinear programming reformulations of MPEC problems, and we gave computational results demonstrating the potential of these tools.

3.6. Supporting research in optimization methods

During the period of this grant we also conducted additional supporting research in various foundation and application areas of optimization and variational analysis. As an example, in the paper entitled, "Constraint nondegeneracy in variational analysis," Robinson studied the sensitivity analysis of variational conditions defined over perturbed systems of finitely many nonlinear inequalities or equations, subject to additional fixed polyhedral constraints. Such conditions can be written as

$$0 \in f(x,u) + N_{S(u)}(x),$$

where N denotes the normal cone and the set $S(u)$ is defined by

$$S(u) = \{x \in P \mid h(x,u) \in Q\}.$$

Thus, S actually depends on a parameter u, as does f, and therefore so do the solutions, if there are any, of this problem. This general framework is a very powerful method for modeling a large class of equilibrium problems, including solutions of the optimality conditions for nonlinear programming but also encompassing many other classes of problems such as complementarity problems. It is more general than the class of variational inequalities, as there is no assumption of convexity on S.

We showed how, if the system of constraints obeys a certain property called *nondegeneracy,* one can construct a local diffeomorphism of the feasible set to its tangent cone. Moreover, this diffeomorphism varies smoothly as the perturbation parameter changes. The original variational condition is then locally equivalent to a variational inequality defined over this (polyhedral convex) tangent cone.

The significance of this transformation lies in the fact that the special case of the variational condition in which the "feasible set" S is a fixed polyhedral convex set is very well understood, and we have a complete set of criteria for good behavior of the solutions of this problem when the function f is perturbed (as S is fixed in that special case, no perturbations appear in it). Thus, what this paper showed is that a very large class of problems with feasible sets that are neither fixed nor polyhedral are really just polyhedral problems in disguise. Accordingly, we can then apply the stability results already known for the well behaved polyhedral case to a substantially more general situation. We can, in fact, predict existence, local uniqueness and Lipschitz continuity, as well as B-differentiability of the solution, by solving a single *affine* variational inequality that is easily computable in terms of the data of the unperturbed problem at the point in question. Operationally, this means that by solving the affine problem, for which we have effective numerical tools, we can estimate locally a solution of the nonlinear problem. The methodology also opens the way to using powerful solution techniques, such as Newton's method, for the nonlinear problems.

Complementing the results in that paper, another paper gives a comprehensive survey of the field of variational conditions with smooth constraints (that is, problems of the above form in which

the functions f and h are of class C^k for suitable k, usually $k = 1$ or 2). It points out areas where current knowledge of these problems is incomplete, particularly in the case of constraints that do not satisfy the nondegeneracy property noted above but do satisfy a weaker property, and it suggests some possible approaches to developing better knowledge about these areas. This paper was prepared as a record of an invited semi-plenary lecture at the triennial International Symposium on Mathematical Programming, held in Copenhagen, Denmark in August 2003, and was published in the special issue of *Mathematical Programming* given to all registrants at that symposium.

Additional supporting research included work on support vector machines, and on slice models (collections of mathematical programming models with the same structure but different data). Examples of slice models appear in data envelopment analysis (DEA) and in cross-validation. By exploiting common structure and shared data we showed how to solve these models much more efficiently than if they had been solved one by one, as is the current practice.

4. Personnel Supported

The following personnel have received salary support from this grant.

- Rikharður Einarsson, Research Assistant
- Michael C. Ferris, Professor
- Julien Granger, Research Assistant
- Jinho Lim, Research Assistant
- Stephen M. Robinson, Professor
- Krung Sinapiromsaran, Research Assistant
- Yi-Chun Tsai, Research Assistant
- Meta M. Voelker, Research Assistant

Of the above, Krung Sinapiromsaran completed the requirements for the Ph.D. in Computer Sciences in October 2000, just at the end of the period of the previous AFOSR grant. He was supported briefly by this grant before resuming duties as a faculty member at Chulalongkorn University, Bangkok, Thailand.

Meta M. Voelker completed the requirements for the Ph.D. in the MACE program (an interdisciplinary program for mathematics in computation and engineering) in December 2002. She accepted an analyst position with Alphatech, Inc., Washington, DC.

Jinho Lim also completed the requirements for the Ph.D. in Industrial Engineering in December 2002. He is now an Assistant Professor in the Industrial Engineering Department of the University of Houston.

5. Publications

The following published papers acknowledge AFOSR support under this grant.

1. J. Almeida, D. Eager, M. Ferris, and M. Vernon, Provisioning content distribution networks for streaming media, in *Proc. 21st Annual Joint Conf. of IEEE Computer and*

Communications Societies (Infocom 2002), June 2002.

2. E.J. Anderson and M.C. Ferris, A direct search algorithm for optimization with noisy function evaluations. *SIAM Journal on Optimization* **11** (2001) 837-857

3. Q. Chen and M.C. Ferris, FATCOP: A fault tolerant Condor-PVM mixed integer program solver. *SIAM Journal on Optimization* **11** (2001) 1019 -1036

4. Q. Chen, M.C. Ferris, and J.T. Linderoth, FATCOP 2.0: Advanced features in an opportunistic mixed integer programming solver. *Annals of Operations Research* **103** (2001) 17-32

5. J.-C. De Bremaecker and M.C. Ferris, A comparison of two algorithms for solving closed crack problems. *Engineering Fracture Mechanics* **66** (2000) 601-605

6. W.D. D'Souza, R.R. Meyer, B.R. Thomadsen, and M.C. Ferris, An iterative sequential mixed-integer approach to automated prostate brachytherapy treatment optimization. *Physics in Medicine and Biology* **46** (2001) 297-322

7. D.L. Eager, M.C. Ferris, and M.K. Vernon, Optimized caching in systems with heterogeneous client populations. *Performance Evaluation* **42** (2000) 163-185

8. M. C. Ferris, J.-H. Lim, and D. M. Shepard, Radiosurgery treatment planning via nonlinear programming. *Annals of Operations Research* 119 (2003) 247—260

9. M. C. Ferris, J.-H. Lim, and D. M. Shepard, Optimization approaches for treatment planning on a Gamma Knife. *SIAM Journal on Optimization* 13 (2003) 921—937

10. M.C. Ferris, M.P. Mesnier, and J. Moré, NEOS and Condor: Solving nonlinear optimization problems over the Internet. *ACM Transactions on Mathematical Software* **26** (2000) 1-18

11. M.C. Ferris and T.S. Munson, Modeling languages and Condor: Metacomputing for optimization. *Mathematical Programming* **88** (2000) 487-506

12. M. C. Ferris and T. S. Munson, Preprocessing complementarity problems. In M.C. Ferris, O.L. Mangasarian, and J.-S. Pang, (editors), *Complementarity: Applications, Algorithms and Extensions,* pp. 143-164. Kluwer Academic Publishers, Dordrecht, The Netherlands, 2001

13. M. C. Ferris and T. S. Munson, Interior point methods for massive support vector machines. *SIAM Journal on Optimization* 13 (2003) 783—804

14. M.C. Ferris, T.S. Munson, and K. Sinapiromsaran, A practical approach to sample-path simulation optimization. In J.A. Joines, R.R. Barton, K. Kang, and P.A. Fishwick, editors, *Proceedings of the 2000 Winter Simulation Conference,* pages 795-804,

Omnipress, Orlando, Florida, 2000

15. M. C. Ferris, G. Pataki, and S. Schmieta, Solving the Seymour problem. *Optima* 66 (2001) 1-7.

16. M.C. Ferris and S.M. Robinson, Enhanced technology for hard optimization problems. In A. Meech, S.M. Veiga, M.M. Veiga, S.R. LeClair, and J.F. Maguire, editors, *Proceedings of the Third International Conference on Intelligent Processing and Manufacturing of Materials (IPMM-2001),* page J, Vancouver, BC, Canada, 2001

17. M.C. Ferris and A. Ruszczynski, Robust path choice and vehicle guidance in networks with failures. *Networks* **35** (2000) 181-194

18. M.C. Ferris and D.M. Shepard, Optimization of Gamma Knife radiosurgery. In D.-Z. Du, P. Pardalos, and J. Wang, editors, *Discrete Mathematical Problems with Medical Applications,* volume 55 of *DIMACS Series in Discrete Mathematics and Theoretical Computer Science,* pages 27-44. American Mathematical Society, Providence, RI, 2000

19. M.C. Ferris and F. Tin-Loi, Limit analysis of frictional block assemblies as a mathematical program with complementarity constraints. *International Journal of Mechanical Sciences* **43** (2001) 209-224

20. M. C. Ferris and M. M. Voelker, Slice models in GAMS, in: P. Chamoni, R. Leisten, A. Martin, J. Minnemann and H. Stadtler, eds, *Operations Research Proceedings 2001*, pp. 239-246, 2002

21. M. C. Ferris and M. M. Voelker, Slice models in general purpose modeling systems: An application to DEA. *Optimization Methods and Software* 17 (2002) 1009—1032

22. J. Granger, A. Krishnamurthy, and S. M. Robinson, Stochastic modeling of airlift operations, in: B. A. Peters, J. S. Smith, D. J. Medeiros, and M. W. Rohrer, eds, *Proceedings of the 2001 Winter Simulation Conference,* pp. 432-440.

23. R. R. Meyer, W. D. D'Souza, M. C. Ferris, and B. R. Thomadsen, MIP models and BB strategies in brachytherapy treatment optimization. *Journal of Global Optimization* 25 (2003) 23—42

24. T.S. Munson, F. Facchinei, M.C. Ferris, A. Fischer, and C. Kanzow, The semismooth algorithm for large scale complementarity problems. *INFORMS Journal on Computing,* 13 (2001)294-311

25. S. M. Robinson, Constraint nondegeneracy in variational analysis. *Mathematics of Operations Research* 28 (2003) 201 – 232

26. S. M. Robinson, Variational conditions with smooth constraints: Structure and analysis. *Mathematical Programming* 97 (2003) 245 – 265

27. S. M. Robinson, "Localized normal maps and the stability of variational conditions." *Set-Valued Analysis* **12** (2004) 259 – 274

28. D. M. Shepard, L. S. Chin, S. J. DiBiase, S. A. Naqvi, J. Lim, and M. C. Ferris, Clinical implementation of an automated planning system for Gamma Knife radiosurgery. *International Journal of Radiation Oncology, Biology, Physics* 56:1488 – 1494, 2003

29. D.M. Shepard, M.C. Ferris, R. Ove, and L. Ma, Inverse treatment planning for gamma knife radiosurgery. *Medical Physics* **27** (2000) 2748-2756

30. D. M. Shepard, Z. Jiang, M. A. Earl, M. C. Ferris, J. Lim, and S. Naqvi. A toolbox for IMRT optimization, *Medical Physics*, 30 (2003) 2320 – 2322

31. K. Sinapiromsaran and M. C. Ferris, Simulation optimization based on a heterogeneous computing environment, In: *Proceedings of the International Conference on Information Technology for the New Millennium* (IConIT2001), pp. 238-248, 2001.

32. H. Zhang, G. Wahba, Y. Lin, M. Voelker, M. Ferris, R. Klein, and B. Klein, Variable selection via basis pursuit for non-Gaussian data. In Proceedings of the ASA Joint Statistical Meetings, 2001, Biometrics Section [CDROM], American Statistical Association, Alexandria, VA, 2001

The following accepted papers acknowledge AFOSR support under this grant.

33. J.-C. De Bremaecker and M. C. Ferris, Numerical models of shear fracture propagation. Accepted by *International Journal of Fracture*

34. J.-C. De Bremaecker, M. C. Ferris, and A. M. Linkov. Including gravity in the displacement discontinuity method when accounting for contact interaction. Accepted by *International Journal of Rock Mechanics and Mining Sciences*

35. M. C. Ferris, S. P. Dirkse, and A. Meeraus, Mathematical programs with equilibrium constraints: Automatic reformulation and solution via constrained optimization. Numerical Analysis Group Research Report NA-02/11, Oxford University Computing Laboratory, Oxford University, 2002. Accepted by *Frontiers in Applied General Equilibrium Modeling: Essays in Honour of Herbert Scarf*

36. M. C. Ferris, R. R. Meyer, and W. D'Souza. Radiation treatment planning: Mixed integer programming formulations and approaches. Accepted by *Handbook of Modelling for Discrete Optimisation*

37. M. C. Ferris and T. S. Munson. Semismooth support vector machines. Accepted by *Mathematical Programming*

38. M. C. Ferris and M. M. Voelker, Fractionation in radiation treatment planning. Accepted by *Mathematical Programming*

39. M. C. Ferris, M.M. Voelker, and H. Zhang. Model building with likelihood basis pursuit. Accepted by *Optimization Methods and Software*

40. J. Granger, A. Krishnamurthy, and S. M. Robinson, Approximation and optimization for stochastic networks, forthcoming in: Y. Ermoliev, K. Marti, and G. Pflug, eds., Proceedings of the IIASA Workshop on Dynamic Stochastic Optimization, Springer-Verlag, 2004

41. J.-H. Lim, M. C. Ferris, and D. M. Shepard. Optimization Tools for Radiation Treatment Planning in Matlab. Accepted by *Handbook of Operations Research/Management Science Applications in Health Care*

42. H. Zhang, G. Wahba, Y. Lin, M. Voelker, M. Ferris, R. Klein, and B. Klein, Variable selection and model building via likelihood basis pursuit. Technical Report 1059, Statistics Department, University of Wisconsin-Madison, Madison, Wisconsin, 2002, accepted by *Journal of American Statistical Association*

The following submitted papers acknowledge AFOSR support under this grant.

43. M. C. Ferris, A. J. Wathen and P. Armand, Limited memory solution of complementarity problems. Revised version of Numerical Analysis Group Research Report NA-02/15, Oxford University Computing Laboratory, Oxford University, 2002. Submitted to *Optimization and Engineering*

44. J. Granger, A. Krishnamurthy, and S. M. Robinson, Rapid improvement of stochastic networks using two-moment approximations. Submitted to *Mathematical and Computer Modelling*

45. J.-H. Lim, M. C. Ferris, S. J. Wright, D. M. Shepard, and M. A. Earl. An optimization framework for conformal radiation treatment planning. Optimization Technical Report 02-10, Computer Sciences Department, University of Wisconsin, Madison, Wisconsin, 2002. Submitted to *INFORMS Journal on Computing*

46. S. M. Robinson, Aspects of the projector on prox-regular sets. Submitted to proceedings of the 2003 Erice Workshop on Variational Analysis and Applications (Eds. F. Giannessi *et al.*), to be published by Kluwer Academic Publishers

In addition, the following Ph.D. dissertations were prepared at the University of Wisconsin-Madison with support from this grant:

47. Meta M. Voelker, Optimization of Slice Models, Dec 2002. Thesis is available at http://www.cs.wisc.edu/~ferris/papers/thesis_voelker.pdf

48. Jin-Ho Lim, Optimization in Radiation Treatment Planning, Dec 2002. Thesis is available as Optimization Technical Report 02-11 at http://www.cs.wisc.edu/math-prog/tech-reports/.

6. Interactions/Transitions

6.1. Participation/presentations at meetings, conferences, seminars, etc.

The following presentations at meetings, conferences, or colloquia involved material related to the research program of this grant.

1. "A practical approach to sample-path simulation optimization" (Ferris), Winter Simulation Conference 2000, Orlando, FL, December 2000

2. "Integrating optimization and simulation: research and practice" (panel discussion) (Robinson), Winter Simulation Conference 2000, Orlando, FL, December 2000

3. "Planning under uncertainty: methods and applications" (Robinson), AFRL/AFOSR program review, Seattle, WA, July 2001

4. "Enhanced technology for hard optimization problems" (Robinson), Conference on Intelligent Processing and Manufacture of Materials (IPMM-2001), Vancouver, BC, Canada, August 2001

5. "Optimization of Gamma Knife Radiosurgery" (Ferris), OR2001, Duisburg, Germany, September 2001

6. "Slice models in general purpose modeling systems" (Voelker), OR2001, Duisburg, Germany, September 2001

7. "Stochastic optimization: Some current opportunities and challenges" (Robinson), Seminar, Department of Electrical and Computer Engineering, University of Wisconsin-Madison, October 2001

8. "Fast improvement of simulated networks" (Robinson), U. S. Army Operations Research Symposium, Ft. Lee, VA, October 2001

9. "Neuro-Dynamic Programming for Radiation Treatment Planning" (Voelker), Oxford University, October 2001

10. "Stochastic Network Modeling of Air Mobility Deployments" (Granger), National Meeting of the Institute for Operations Research and the Management Sciences

(INFORMS), Miami Beach, FL, November 2001

11. "Solution of Massive Support Vector Machine Problems" (Ferris), Oxford University, Oxford, November 2001

12. "Optimization of Gamma Knife Radiosurgery" (Ferris), University of North Carolina, November 2001

13. "Neuro-Dynamic Programming for Radiation Treatment Planning" (Ferris), GAMS Corporation, November 2001

14. "Optimization of Gamma Knife Radiosurgery" (Ferris), Georgia Institute of Technology, November 2001

15. "Optimization of Gamma Knife Radiosurgery" (Ferris), Cambridge University, November 2001

16. "Stochastic modeling of airlift operations" (Granger), Winter Simulation Conference 2001, Arlington, VA, December 2001

17. "Modeling, Simulations and Optimization" (Ferris), Workshop on Optimization for Computational Fluid Dynamics, Oxford University, December 2001

18. "Neuro-Dynamic Programming for Radiation Treatment Planning" (Ferris), University of Kaiserslautern, Germany, February 2002

19. "Neuro-Dynamic Programming for Radiation Treatment Planning" (Ferris), Dundee University, March 2002

20. "Approximation and optimization for stochastic networks" (Robinson), Workshop on Dynamic Stochastic Optimization, International Institute for Applied Systems Analysis, Laxenburg, Austria, March 2002

21. "MPEC: Automatic reformulation and solution via constrained NLP" (Ferris), Cowles Foundation, Yale University, April 2002

22. "Optimization of Gamma Knife Radiosurgery" (Ferris), CORE, Belgium, April 2002.
23. "Complementarity theory, applications and algorithms" (Ferris), London School of Economics, May 2002

24. "Neuro-Dynamic Programming for Radiation Treatment Planning" (Ferris), SIAM Meeting on Optimization, Toronto, May 2002

25. "Optimization of Gamma Knife Radiosurgery" (Ferris), Edinburgh University, June 2002

26. "Conformal Radiation Treatment Planning" (Ferris), John Radcliffe Infirmary, Oxford, June 2002

27. "Nondegeneracy and the variational condition" (Robinson), Joint Meeting of the American Mathematical Society and the Unione Matematica Italiana, Pisa, Italy, June 2002

28. "Planning under uncertainty: Methods and applications" (Robinson), AFRL Electronic Prototyping Review, Sunnyvale, CA, July 2002

29. "Complementarity Solvers: Now and Beyond" (Ferris), International Conference on Complementarity 2002, Cambridge University, July 2002

30. "An optimization tool for conformal radiotherapy" (Lim), MOPTA conference, McMaster University, Hamilton, Ontario, Canada, August 2002.

31. Colloquium lecture (Robinson), Statistical Sciences Group, Los Alamos National Laboratory, Los Alamos, NM, October 2002

32. "Optimization of Gamma Knife Radiosurgery" (Lim), INFORMS National Meeting, San José, CA, November 2002

33. "Neuro-Dynamic Programming for Radiation Treatment Planning" (Voelker), INFORMS National Meeting, San José, CA, November 2002

34. "Stereotactic Radiosurgery" (Ferris), First International Workshop on Optimization in Radiation Therapy, Fort Lauderdale, FL, January 2003

35. "Conformal Radiation Therapy" (Lim), First International Workshop on Optimization in Radiation Therapy, Fort Lauderdale, FL, January 2003

36. "Fractionation in Radiation Therapy: An Optimization Approach" (Ferris), First International Workshop on Optimization in Radiation Therapy, Fort Lauderdale, January 2003

37. "Fractionation in Radiation Therapy: An Optimization Approach" (Ferris), DIMACS, Rutgers University, New Jersey, March 2003

38. "Radiation Therapy, Computer Aided Surgery and Optimization: A View of the Future" (Ferris), Panel Member, DIMACS, Rutgers University, New Jersey, March 2003

39. "Constraint degeneracy in variational conditions," (Robinson), Workshop on Variational Analysis and Applications, Ettore Majorana Foundation and Centre for Scientific Culture, Erice (Sicily), Italy, June 2003

40. "Optimization of Gamma Knife Radiosurgery" (Ferris), University of Limoges, Limoges, France, June 2003

41. "Complementarity theory, applications and algorithms" (Ferris), University of Limoges, Limoges, France, June 2003

42. "Fractionation in Radiation Therapy: An Optimization Approach" (Ferris), University of Limoges, Limoges, June 2003

43. "Optimization of Gamma Knife Radiosurgery" (Ferris), Université Paul Sabatier, Toulouse, France, June 2003

44. "Fractionation in Radiation Therapy: An Optimization Approach" (Ferris), International Symposium on Mathematical Programming, Copenhagen, Denmark, August 2003

45. "Mathematical Programs with Equilibrium Constraints: Automatic Reformulation and Solution via Constrained Optimization" (Dirkse), International Symposium on Mathematical Programming, Copenhagen, Denmark, August 2003

46. "Variational conditions with smooth constraints: Structure and analysis" (Robinson), invited semi-plenary lecture, International Symposium on Mathematical Programming, Copenhagen, Denmark, August 2003

47. "Global Optimization Problems in Medicine" (Ferris), Global Optimization Institute, Argonne National Laboratories, September 2003

48. "Fractionation in Radiation Therapy"(Ferris), CIBM (Computation and Informatics in Biology and Medicine), Madison, September 2003

49. "Optimization of Gamma Knife Radiosurgery" (Ferris), General Algebraic Modeling System Workshop, Washington D.C., September 2003

50. "Mathematical Programs with Equilibrium Constraints: Automatic Reformulation and Solution via Constrained Optimization" (Ferris), Workshop on Numerical Computation in Economics, Federal Reserve Bank of Chicago, December 2003

6.2. Consultative and advisory functions to other laboratories and agencies

From Fall 2001, Robinson has served as a member of the Board on Mathematical Sciences and Their Applications, National Research Council. In that capacity he has worked to focus part of the Board's program on the improvement of modeling and simulation in the Department of Defense and the Services. This has involved substantial contacts with DoD agencies including the Defense Modeling and Simulation Office (DMSO), Army Models and Simulation Office (AMSO), and the Future Combat Systems (FCS) Program.

6.3. Transitions

The planning methodology developed under this and predecessor grants for the Gamma Knife radiosurgery device is in use on patients at the University of Maryland Medical School. The tool is being used in day-to-day planning without the intervention of any of its authors.

As described in Section 3.1.3, we have developed a suite of optimization tools to facilitate radiation treatment planning within the Matlab programming environment. These tools and the associated data are posted on http://www.cs.wisc.edu/~ferris/3dcrt and are available to anyone for download and use.

7. New discoveries, inventions, or patent disclosures

None during the period of this grant. After the end of the grant period, the University of Maryland Medical School began the procedure to apply for a patent related to the Gamma Knife work reported here.

8. Honors/Awards

Awards during the period of this grant:

- Ferris received a Guggenheim Fellowship for the period 2001-2002. In connection with this award he held a Visiting Fellowship at Exeter College, Oxford University, England to August 2002.
- In June 2001 Robinson received the John K. Walker, Jr. Award from the Military Operations Research Society (MORS).
- In November 2002 Ferris, with J. H. Lim and D. M. Shepard, received the William Pierskalla Best Paper Award for research excellence in the field of health care management science. AFOSR sponsored the research recognized by this award. The award was presented at the National Meeting of the Institute for Operations Research and the Management Sciences (INFORMS), in San José, CA.

Former awards (lifetime achievement honors) of the principal investigators include:

- Doctor *honoris causa,* University of Zürich, Switzerland, April 1996 (Robinson)
- George B. Dantzig Prize, Mathematical Programming Society (MPS) and the Society for Industrial and Applied Mathematics (SIAM), July 1997 (Robinson)
- Beale-Orchard-Hays Prize, Mathematical Programming Society (MPS), August 1997 (Ferris)